ANALYTICAL METHOD DEVELOPMENT AND VALIDATION FOR THE ESTIMATION OF NOVEL PHARMACEUTICAL API AND ITS DOSAGE FORM BY USING QUALITY BY DESIGN APPROACH

SYNOPSIS

SUBMITTED TO THE

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED

FOR THE CONSIDERATION OF REGISTRATION FOR THE DEGREE

OF

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL SCIENCES

UNDER

THE FACULTY OF SCIENCE AND TECHNOLOGY

BY

Ms. Prachi Anurath Kalyankar

M. Pharm

UNDER THE GUIDANCE OF

Dr. R.S. Moon

M. Pharm, Ph.D.

Assistant Professor,

School of Pharmacy

SWAMI RAMANAND TEERTH MARATHWADA UNIVERSITY, NANDED-431606

2024-25

Sr. No.	Content	Page No.
1.	Introduction	2
2.	Rational of research work	7
3.	Review of literature	8
4.	Importance of study	13
5.	Aim and Objective	14
6.	Research Methodology	15
7.	Research work plan	16
8.	Outcome of research	16
9.	References	17

1. INTRODUCTION:

The pharmaceutical sector is concerned with product efficacy, safety, and quality. FDA decided to implement various Designs of Experiments (DoE) in the pharmaceutical industries. Quality by Design helps in the development of high- quality products and guides to manage product quality across its entire life cycle. This method quickly gains popularity worldwide due to its many benefits and use of numerous high-quality statistical tools. QbD is a meticulous, proactive, risk-based strategy for pharmaceutical development that commences with predetermined goals and emphasizes product and process understanding and process control based on reliable research. The QTPP, knowledge of product and process design, scale-up, control strategy, and constant improvement are considered as crucial components of pharmaceutical QbD. After approval, during the product lifecycle management process, the competency of the product and the process is evaluated and continuously enhanced. One of the fundamental criteria is "Quality", along with the safety and efficacy for any entity to be considered and approved as a drug. The pharmaceutical sector has always struggled to provide high-quality drug products. Major problems with the poor quality of pharmaceutical products can be ascribed to several factors, including variable starting materials, a lack of manufacturing process automation and control and erroneous knowledge regarding the product and process characteristics. The principal sources of variability associated with the development of pharmaceutical goods are shown in Fig. 1.1

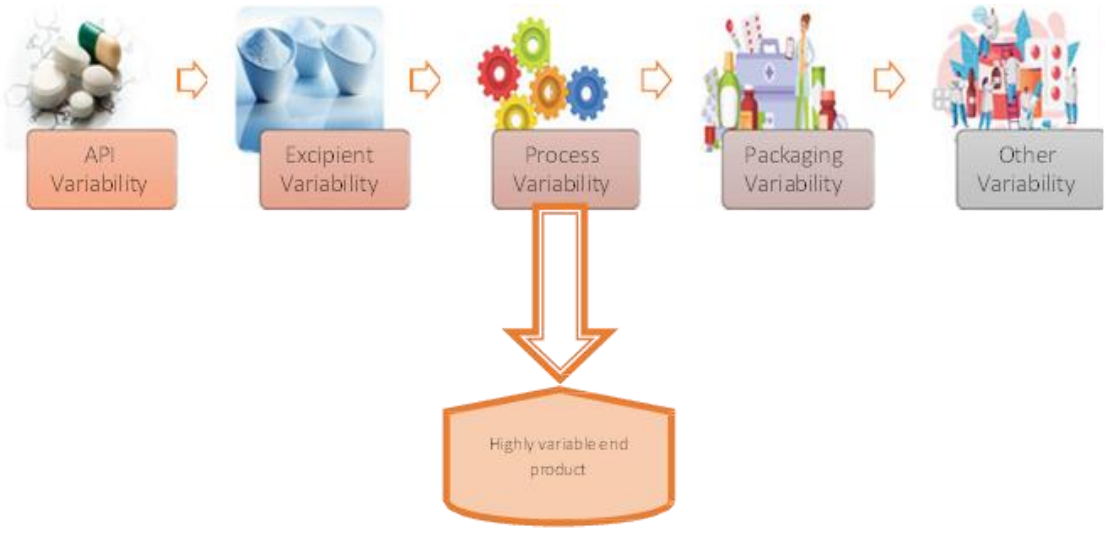

Fig. 1.1 Sources that contribute to quality variation among pharmaceutical products

Recently the concept of "Quality by Design" (QbD) gaining much attention among pharmaceutical industries for maintaining Quality. It serves as a bridge between industry and drug regulatory authorities to move towards a scientific, risk based, holistic and proactive approach for development of pharmaceutical product. It mainly covers designing and developing formulations and manufacturing processes to ensure predefined product quality [6].

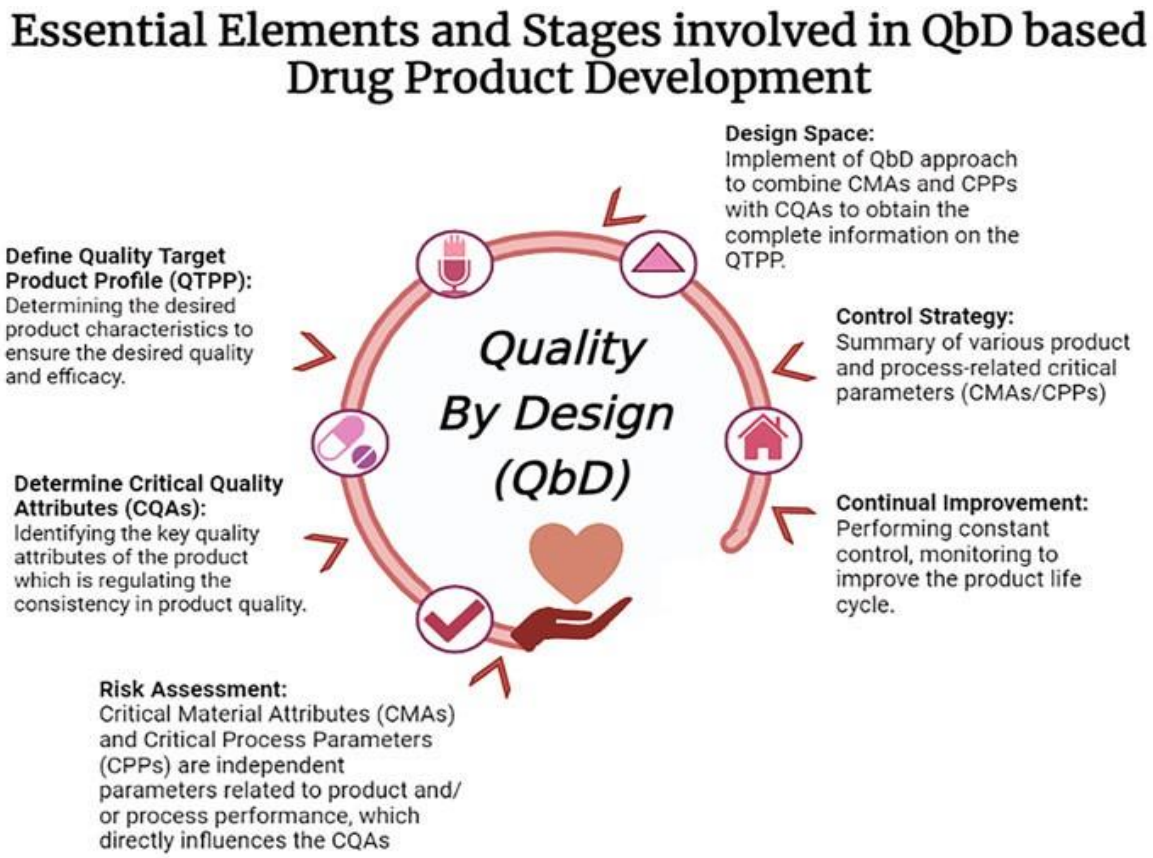
Essential Elements and Stages involved in QbD based Drug Product Development
Design Space:
Implement of QbD approach to combine CMAs and CPPs with CQAs to obtain the complete information on the QTPP.
Define Quality Target Product Profile (QTPP):
Determining the desired product characteristics to ensure the desired quality and efficacy.
Quality By Design (QbD)
Control Strategy:
Summary of various product and process-related critical parameters (CMAs/CPPs)
Determine Critical Quality Attributes (CQAs):
Identifying the key quality attributes of the product which is regulating the consistency in product quality.
Continual Improvement:
Performing constant control, monitoring to improve the product life cycle.
Risk Assessment:
Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs) are independent parameters related to product and/ or process performance, which directly influences the CQAs

Fig. 1.2 Essential elements and stages involved in QbD

Some of the QbD elements include defining target product quality profile, designing product and manufacturing processes, identifying critical quality attributes, process parameters, and sources of variability & controlling manufacturing processes to produce consistent quality over time The purpose of this article is to discuss the concept of pharmaceutical Quality by Design and describe how it can be help to ensure pharmaceutical quality & drug development [6].

1.1 Key characteristics of QbD [6]

- A tool for focused & efficient drug development
- Dynamic and systematic process
- Relies on the concept that Quality can be built in as a continuum
- It is applicable to Drug Product and Drug Substance development (chemicals / biologics)
- It is applicable to analytical methods
- Can implemented partially or totally
- Can be used at any time in the life cycle of the Drug
- Always encouraged by Regulators.

1.2 Benefits of QbD [1]

- Implementation of QbD helps to develop rugged and robust/strong method that helps to go with ICH guidelines hence for that reason pharmaceutical industries are adopting this concept of QbD. This approach facilitates continuous improvement in method
- Chromatographic techniques like HPLC (For stability studies, method development, and determination of impurities in pharmaceutical)
- Eliminate batch failures
- Minimize deviations and costly investigations
- Avoid regulatory compliance problems
- Empowerment of technical staff
- Efficient, agile, flexible system
- Increase manufacturing efficiency, reduce costs and project rejections and waste
- Build scientific knowledge base for all products
- Better interact with industry on science issues
- Ensure consistent information
- Incorporate risk management
- Reduce end-product testing

QbD is defined in ICH guidelines Q8(R2) as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management" ICH guidelines suggest quality in the design to eliminate risk or failures of the process and thus the product. In this approach, the quality associated process variables are defined, their interactions studied, control strategy implemented, and finally, the method is continually monitored [10].

The analytical method development for a drug is also a process, and quality principles in the ICH guidelines can be implemented in the design of the method development.

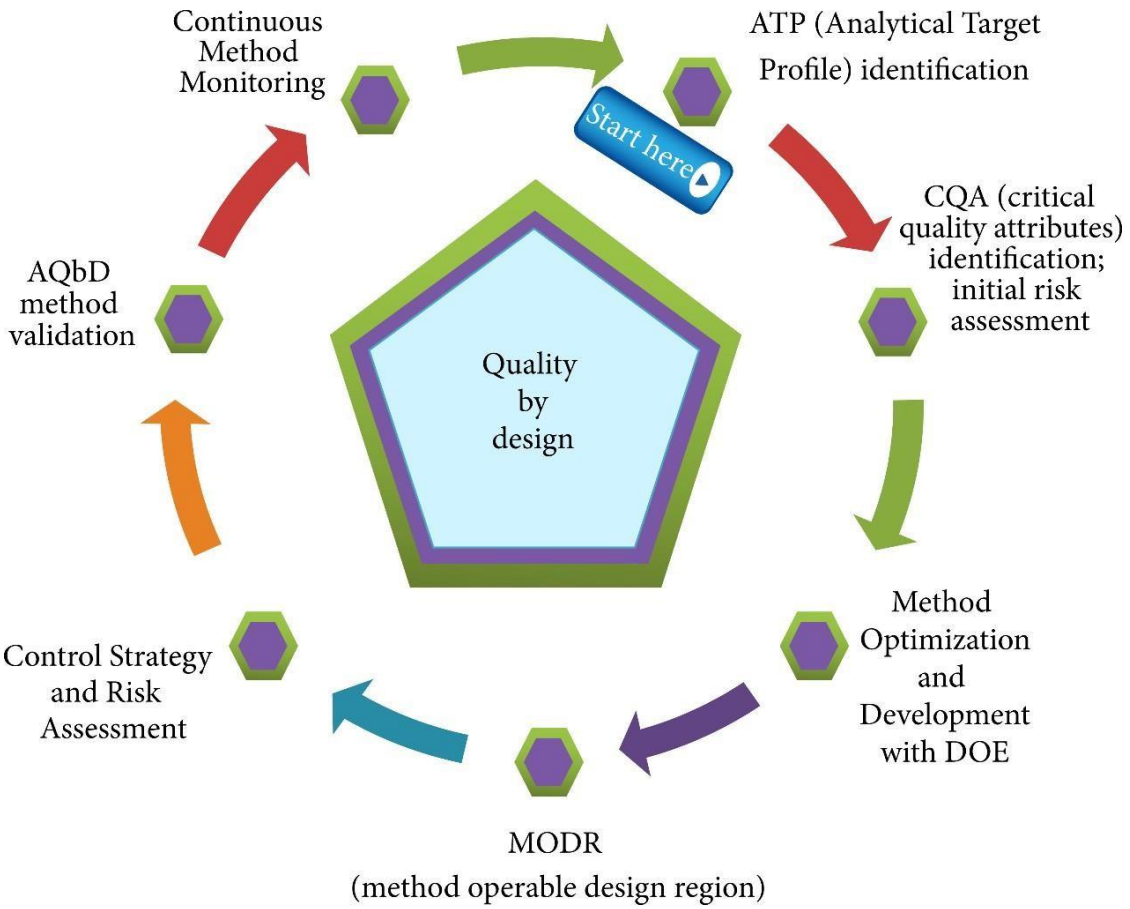
Continuous Method Monitoring
ATP (Analytical Target Profile) identification
Start here
CQA (critical quality attributes) identification; initial risk assessment
AQbD method validation
Quality by design
Method Optimization and Development with DOE
Control Strategy and Risk Assessment
MODR
(method operable design region)

Figure 1.3: A QbD tools and life cycle.

1.3 Steps involved in analytical development by QbD approach [10]

- ATP (Analytical Target Profile) identification
- CQA identification, Initial Risk Assessment
- Method Optimization and development with DOE
- MODR (Method Operable Design Region
- Control Strategy with Risk assessment
- A QbD Method Validation
- Continuous Method Monitoring

2. RATIONALE OF RESARCH WORK

- we have decided to work on the Analytical method development and validation for the estimation of novel pharmaceutical API and its dosage form by using QbD approach.
- Pharmaceutical industry has focused on product Quality, Safety, and Efficacy. Product quality has been increasing by implementing scientific tools such as QbD (Quality by Design) and PAT (Process Analytical Technology). Scientific approaches will provide the clear and sufficient knowledge from product development to manufacturing.
- These QbD tools will minimize the risk by increasing the productivity and quality. Nowadays QbD approach has been successfully implemented in generic formulation development.
- Present study will indicate the importance of QbD approach in method development and validation of the pharmaceutical product which increase quality of medicine.

3. REVIEW OF LITRATURE

Pittu K Chaitanya Reddy et al., **[11] (2022**) A simple, sensitive, precise, accurate, and robust, high-performance liquid chromatographic method has been developed to simultaneously estimate Metformin (MET) and Dapagliflozin (DAPA) in pharmaceutical formulation. Design of experiments (DoE) was applied for multivariate optimization of the experimental conditions of the RPHPLC method. A risk assessment was performed to identify the critical method parameters. The mobile phase composition, flow rate, and column temperature were used to design mathematical models. Box Behnken design (BBD) was used to study the response surface methodology and the effects of these independent factors. The desirability function was used to simultaneously optimize the retention time and resolution of MET and DAPA. The optimized and predicted data from the contour diagram consisted of acetonitrile and ortho phosphoric acid (0.1%) in the ratio of 50:50, respectively, at a flow rate of 1.0 ml/min and column temperature 29°C. Using these optimum conditions, baseline separation of both drugs with good resolution and run time of less than 5 min were achieved. The optimized assay conditions were validated according to ICH guidelines. Hence, the results clearly showed that the Quality by design approach could be successfully applied to optimize the RP-HPLC method for simultaneous estimation of MET and DAPA.

A.R. Jaybhave et al.,**[12] (2021)** had reported A simple, sensitive and reproducible spectrophotometric method is developed for determining the Tenofovir Disoproxil Fumarate content in bulk and in tablet dosage form using an experimental design approach. Quality by design (QbD) refers to the achievement of certain predictable quality with desired and predetermined specifications. A very useful component of the QbD is the understanding of factors and their interaction effects by a desired set of experiments. The present study describes the development of a comprehensive science and risk-based RP-HPLC method and subsequent validation for the analysis of Tenofovir Disoproxil Fumarate active pharmaceutical ingredient (API) and Tablet using a quality by design approach. The described method was linear. (r2=0.99).

Vancha Harish et al., **[13] (2022)** had reported he analytical quality by design (AQbD) approach is utilized for developing and validating the simple, sensitive, cost-effective reverse-phase high performance liquid chromatographic method for the estimation of xanthohumol (XH) in bulk and nanoformulations. The Box–Behnken design (BBD) is applied for method optimization. The mobile phase ratio, pH and flow rate were selected as independent variables, whereas retention time, peak area, peak height, tailing factor, and theoretical plates were selected as dependent variables. The chromatogram of XH obtained under optimized conditions has given optimum conditions such as retention time (5.392 min), peak area (1,226,737 mAU), peak height (90,121 AU), tailing factor (0.991) and theoretical plates (4446.667), which are contoured in the predicted values shown by BBD. Validation of the method has been performed according to ICH Q2(R1) recommendations, using optimized conditions for linearity, limit of detection (LOD) and limit of quantification (LOQ), accuracy, precision, robustness and system suitability.

Krunal Y. Patel et al.,**[16] (2021)** had reported the experimental design based on central composite design of two key components of the RPHPLC method (mobile phase and pH) is presented. The chromatographic conditions were optimized with the Design Expert software 11.0 version, i.e., Phenomenex ODS column C18 (250 mm × 4.6 mm, 5.0 μ), mobile phase used acetonitrile to water (0.01% triethylamine with pH 6.5) (70:30, v/v), and the flow rate was 1 ml/min with retention time 4.15 min. The developed method was found to be linear with r2 = 0.991 for range of 10–200 μg/ml at 270 nm detection wavelength. The system suitability test parameters, tailing factor and theoretical plates, were found to be 1.49 and 5236. The % RSD for intraday and inter day precision was found to be 0.70–0.94 and 0.55– 0.95 respectively. The robustness values were less than 2%. The assay was found to be 99.73 ± 0.61%.

***Mousa Sha'at et al.,*[14] (2022)** had reported quality by design (QbD)-enabled development of a simple, rapid, precise, accurate, and cost-effective high-performance liquid chromatographic method for estimation of metformin hydrochloride (M-HCl). Design of experiments (DoE) was applied for multivariate optimization of the experimental conditions of the HPLC method. Risk assessment was performed to identify the critical method parameters (CMPs) using Ishikawa diagram. The factor screening studies were performed using a two-factor three-levels design. Two independent factors, buffer pH and mobile phase composition, were used to design mathematical models. Central composite design (CCD) was used to study the response surface methodology and to study in depth the effects of these independent factors, thus evaluating the critical analytical attributes (CAAs), namely, retention time, peak area, and symmetry factor as the parameters of method robustness. Desirability function was used to simultaneously optimize the CAAs. The optimized and predicted data from contour diagram consisted of 0.02 M acetate buffer pH = 3/methanol in a ratio of 70/30 (v/v) as the mobile phase with a flow rate 1 mL/min. The separation was made on a Thermoscientific ODS HypersylTM chromatographic column (250 × 4.6 mm, 5 µm) with oven temperature 35 ◦C and UV detection at 235 nm. The optimized assay conditions were validated according to ICH guidelines. Hence, the results clearly showed that QbD approach could be successfully applied to optimize HPLC method for estimation of M-HCl.

***R.S. Sakhare et al.,*[19] (2023)** had reported the Quality by Design" (QbD) serves as a bridge between industry and drug regulatory authorities to move towards a scientific, risk based holistic and proactive approach for development of pharmaceutical products. So, the present work describes the development of RP-HPLC method for simultaneous estimation of azelnidipine and telmisartan in pharmaceutical dosage form by QbD approach. The Box-Behnken design was used for screening where the effect of flow rate, % organic phase and temperature on retention time, resolution, number of theoretical plates (NTP) and symmetry factor (critical quality attributes) was evaluated. Chromatogram was run through Discovery C18 250 x 4.6 mm, 5µ. Mobile phase containing 0.01N Ortho Phosphoric Acid: Acetonitrile taken in the ratio of 53.8:46.2V/V was pumped through column at a flow rate of 0.9 ml/min. The developed method was validated according to guidelines of the (ICH).

***Tim Tome et al.,*[17] (2021)** had reported e Analytical Quality by Design (AQbD) concept, an extension of Quality by Design (QbD), which was introduced in 2004 by the U.S. Food and Drug Administration (FDA) and approved in 2005 by the International Conference on Harmonization (ICH). AQbD is a systematic approach to method development, controlling all stages of the analytical procedure life cycle. It includes a definition of the analytical target profile (ATP), identification of critical method parameters or factors, and selection of critical method attributes (CMAs) or responses. Screening and response-surface experimental designs allow the recognition of significant factors and their optimization by statistical analysis. The factor− response relationship is described by a mathematical model, which is able to predict the optimal response. Multivariate combinations of factors fulfilling the CMA requirements are presented in the design space or method operable design region (MODR), where robust method performance is ensured.

***Amit Vitthal Babar et al.,*[18] (2022)** had reported the number of new drugs introduced into the market is increasing day by day. These drugs may be either new entities or partial structural modification of the existing one. Very often there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. This happens because of the possible uncertainties in the continuous and wider usage of these drugs, reports of new toxicities (resulting in their withdrawal from the market), development of patient resistance and introduction of better drugs by competitors. Under these conditions, standards and analytical procedures for these drugs may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical methods for such drugs

***Kishor S. Arote et al.,*[21] (2022)** had reported the QbD approach for analytical method development and describes the implementation of QbD in analytical procedure validation. High performance liquid chromatography is most accurate methods widely used for the qualitative and quantitative analysis of drug product. HPLC is an analytical tool which is able to detect, separate and quantify the drug, its various impurities and drug related degradants that can be generate on synthesis or storage. Method development is essential for discovery and evaluation of drugs in the pharmaceutical formulation. HPLC method development depends on chemical structure of the molecules, synthetic route, solubility, polarity, pH and pKa values, and functional groups

activity etc. functional groups activity etc. Validation of HPLC method as per ICH Guidelines gives information regarding various stages and knowing characteristics like Accuracy, specificity, linearity, limit of detection, ruggedness, robustness limit of quantification. Quality by Design (QbD) is a methodology of pharmaceutical development, recommended by regulatory agencies like USFDA.

4. IMPORTANCE OF THE STUDY

- Quality by design is an approach that aim to ensure the quality of the medicine by employing statistical, analytical and risk-management methodology in design, development and manufacturing of medicine.
- Present study indicates importance of QbD approach in method development and validation for the estimation of the pharmaceutical product which increase quality of medicine.

5. AIM AND OBJECTIVES

AIM:

- Analytical method development and validation for the estimation of novel pharmaceutical API and its dosage form by using quality by design approach.

OBJECTIVES:

- To develop RP-HPLC method for some drugs and its formulation.
- To apply QbD approach using statistical experimental design (DoE) to develop a robust method.
- To validate the developed methods according to ICH Q2(R1) Guidelines for the following parameter:

- Accuracy
- Linearity
- Precision
- LOD (limit of detection)
- LOQ (Limit of Quantification)
- Specificity
- Robustness

6. RESEARCH METHODOLOGY

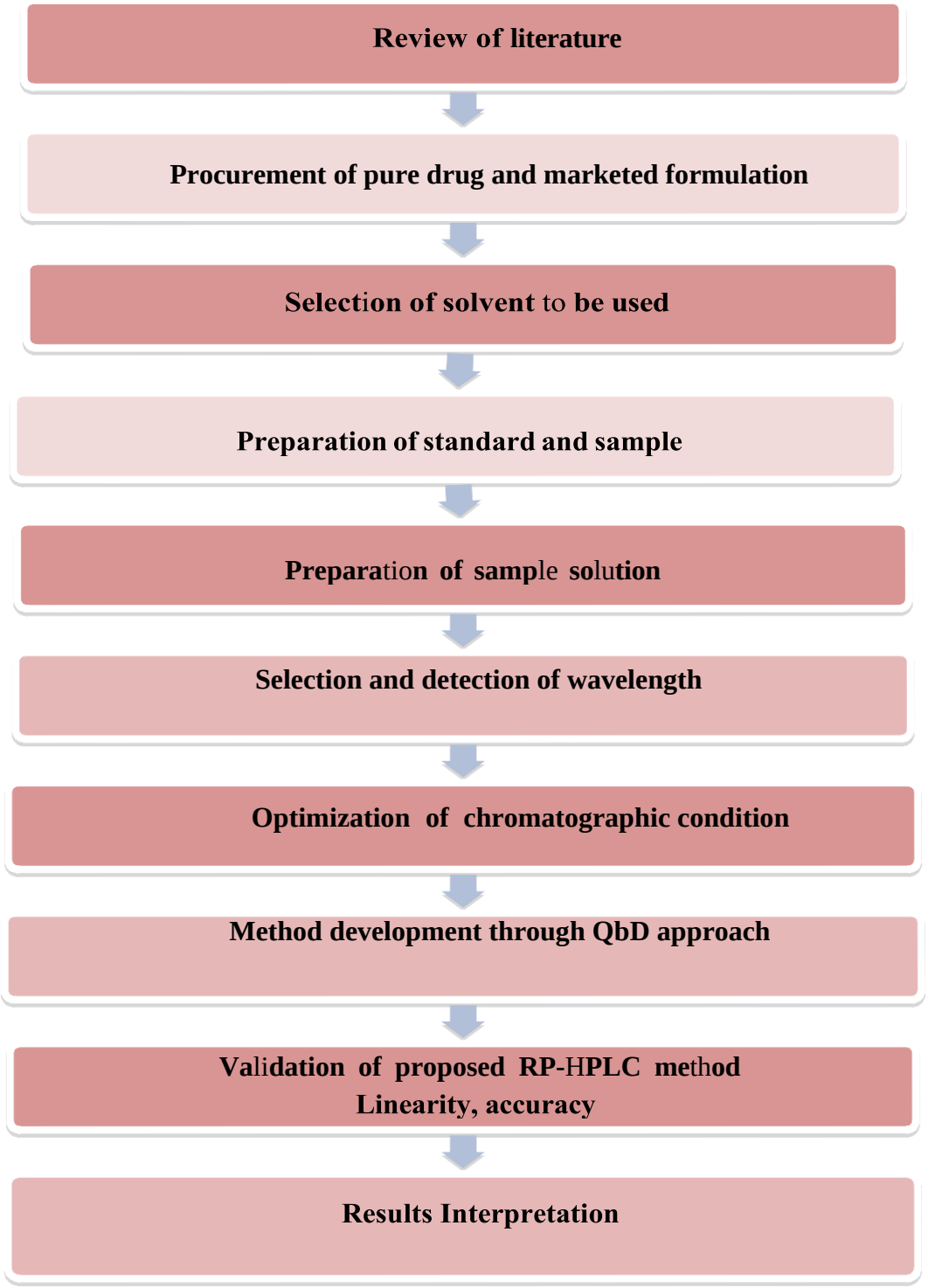
Review of literature
Procurement of pure drug and marketed formulation
Selection of solvent to be used
Preparation of standard and sample
Preparation of sample solution
Selection and detection of wavelength
Optimization of chromatographic condition
Method development through QbD approach
Validation of proposed RP-HPLC method
Linearity, accuracy
Results Interpretation

Figure 2: Flow chart of research methodology use.

7. RESEARCH WORK PLAN

Sr. No.	Work	Period
1.	Literature survey	6 months
2.	Procurement of API and Excipients	3 months
3.	Selection of solvent to be used	1 months
4.	Preparation of standard stock solution and sample solution	1 months
5.	Selection of wavelength and Preparation and selection of mobile phase	3 months
6.	Optimization of chromatographic conditions	3 months
7.	Implementation of Quality by design approach	6 months
8.	Validation of propose RP-HPLC method	6 months
9.	Other suggested work and compilation of data	7 months
	Total duration of work	**36 months**

8. OUTCOME OF RESEARCH

- Understanding of QbD approach for analytical method development and validation for the estimation of drugs and its formulations.
- Validation of developed method as per ICH Q2(R1) Guidelines.

9. REFERENCES

1. Gandhi A, Roy C; Quality by Design (QbD) in pharmaceutical industry: Tools, perspective and Challenges; pharma Tutor; 2016; 4(11); 12-20
2. Woodcock J, The concept of pharmaceutical quality. American Pharmaceutical Review 2004;7: 10–15.
3. Q9: Quality Risk Management. ICH Harmonized Tripartite Guidelines International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006
4. Q10: Pharmaceutical Quality System, ICH Tripartite Guidelines. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
5. Q8 (R1): Pharmaceutical Development, Revision 1, ICH Harmonized Tripartite Guidelines, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2007.
6. Chandrakantsingh Vijaysing Pardeshi, Dipak Bari, Ganesh Shevalkar, Vikas Singhai Introduction to Qulaity by Desing , 2024
7. Nadpara NP, Thumar RV, Kalola VN, Patel PB. Quality By Design (QbD) : A Complete Review. Int. J. Pharm. Sci. Rev. Res. 2012; 17: 20-28.
8. Pohl M, Schweitzer M, Hansen G, Hanna BM, Borman P, Smith K, Larew J, Nethercote P. Implications and opportunities of applying the principles of QbD to analytical measurements. Pharm. Technol. Eur. 2010; 22: 29–36.
9. Eziokwu NV. Quality by design (QbD): manufacturing and product quality of Generics drugs perspective. Journal of Global Trends in Pharmaceutical Sciences 2013;4: 1257-1262.
10. N. V. V. S. S. Raman, Useni Reddy Mallu, and Hanimi Reddy Bapatu A review on Analytical Quality by Design Approach to Test Method Development and Validation in Drug Substance Manufacturing. Hindawi Publishing Corporation Journal of Chemistry 2015; Article ID 435129, 1-8.

,

11. Pittu K Chaitnya Reddy, Dr. Priyanka Mathur, A QBD driven analytical method development and Validation of metformin and Dapagliflozin by Using RP-HPLC, International Journal of Health science,6(S4),8237-8248.
12. A.R. Jaybhave, M. Shinde, R. Mogal, S. Narkhede, Dr.A. Jadhav , QbD approach to analytical RP-HPLC method Development and validation of tenofovir disoproxil fumarate in Dosage form, Journal of pharmaceutical science an research,Vol.13(7),381-386.
13. Vancha Harish Waleed Hassan Almalki, Quality by Design based method for estimation of Xanthohumol in bulk and solid lipid nanoparticles and validation, Molecules 2023,28,472.
14. Mousa Sha ‘at, Adrian Florin Spac, Iulian Stoleriu, Alexandra Bujor, Implementation of QbD approach to the analytical method development and validation of the estimation of metformin hydrochloride in tablet dosage form by HPLC, Pharmaceutics2022,14.1187.
15. Gandhi A, Roy C; Quality by Design (QbD) in pharmaceutical industry: Tools, perspective and Challenges; pharma Tutor; 2016; 4(11); 12-20
16. Krunal Y. Patel, Zarna R. Dedania, Ronak R. Dedani. QbD approach to HPLC method development and validation of ceftriaxone sodium, Future Journal of Pharmaceutical Science (2021) 7:141.
17. Tim Tome, Nina zigart, Zdenko Casar, and Ales Obreza, Development and Optimization of Liquid chromatography analytical method by using AqbD principle: Overview and recent advances, Organic Process research and development,2019,23,1784-1802. S.
18. Amit Vitthal Babar, Dr. Gaurav Jain, Jeevan Patel, Ramakant Sharma, Shabnam Khan, Dr. Rakesh Patel, QBD approach in HPLC method development and Validation of Tamoxifen, International Journal of Pharmaceutical Science and Medicine, Vol.7Issue.9, September-2022, pg.90-105.
19. R.S. Sakhare, M.D. Padole, S.S. Tondare, A.H. Gaherwar, M.H. Muratkar, RP-HPLC method Developemnet and validation for Simultaneous estimation of azelidipine and telmisartan in pharmaceutical dosage form by QBD approach, International Journal of Pharmaceutical science and research ,2023; Vol.14(12):5760-5770.

20. Vogt, et al. “Development of Quality By-Design Analytical Methods,” Journal of Pharmaceutical Sciences Vol. 100, No. 3, p.797-812, March 2011
21. Kishor S. Arote, darshan A. Salade, Nilesh V. Patil, Dr. Vikas Pawar, A review on: analytical method development and validation and its QbD approach, International Journal of novel research and Development,2022, Volume 7, Issue9 September 2022 ISSN 2456-4184.

Date:

Place: Nanded

Ms. Prachi Anurath Kalyankar — **Research Scholar**

Dr. R.S. Moon — **Assistant Professor**